Review Article

Unconventional T cells – New players in antifungal immunity

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ABSTRACT

Life-threatening invasive fungal diseases (IFD) are increasing in incidence, especially in immunocompromised patients and successful resolution of IFD requires a variety of different immune cells. With the limited repertoire of available antifungal drugs there is a need for more effective therapeutic strategies. This review interrogates the evidence on the human immune response to the main pathogens driving IFD, with a focus on the role of unconventional lymphocytes e.g. natural killer (NK) cells, gamma/delta (γδ) T cells, mucosal associated invariant T (MAIT) cells, invariant natural killer T (iNKT) cells and innate lymphoid cells (ILC). Recent discoveries and new insights into the roles of these novel lymphocyte groups in antifungal immunity will be discussed, and we will explore how an improved understanding of antifungal action by lymphocytes can inform efforts to improve antifungal treatment options.

1. Introduction

Invasive fungal diseases (IFD) present a growing problem with the increasing use of immunosuppressive drugs and immunomodulatory therapies [1,2]. The predominant causes of IFDs are *Aspergillus* spp., *Candida* spp.*, Cryptococcus neoformans* and *Pneumocystis jirovecii*, which together account for 90% of deaths from fungal disease [3]. IFDs are typically named after the causative pathogen: for example, *Candida*, *Aspergillus*, *Cryptococcus*, *P. jirovecii*, and *Histoplasma* cause candidiasis, aspergillosis, cryptococcosis, *Pneumocystis jirovecii* pneumonia, and histoplasmosis, respectively. *Candida* species and *Pneumocystis jirovecii* are well-adapted to the human body and form part of the host microbiota even in healthy individuals [4,5]. In contrast, most other invasive fungal pathogens are environmental microbes. Infection of humans may occur through inhalation or even direct, possibly traumatic, inoculation. The important pathogens *Cryptococcus* and *Aspergillus* as well as endemic fungal pathogens such as *Histoplasma* or *Coccidioides* spp. almost exclusively infect the host through inhalation of infectious airborne spores [6]. IFDs are rare in healthy individuals, and exacerbation of an IFD is typically associated with immunosuppression and other conditions which result in impaired immunity, such as hematologic malignancies, HIV, inherited genetic diseases and chronic allergic pulmonary diseases [7,8]. Furthermore, disruption of natural barriers, for example anastomotic leakage after abdominal surgery or indwelling vascular catheters, promotes infections such as candidiasis [9].

The immune response to fungal pathogens involves many types of immune cells. The individual importance of certain immune cell types and their respective immune responses vary greatly depending on the specific fungal pathogen. For example, IFDs caused by *Cryptococcus* and *Pneumocystis* mainly occur in patients who suffer from CD4 T cell depletion caused by HIV [10,11]. In contrast, neutrophil dysfunction or neutropenia are identified as a leading host factor increasing the risk for invasive aspergillosis and candidiasis [7]. Nevertheless, there is increasing evidence that lymphocytes also play an important role in the host defence against *Aspergillus* and *Candida* diseases [12].

The majority of reviews on lymphocyte-mediated antifungal immunity have focused more on contributions from the adaptive immune system, i.e. conventional CD4 and CD8 T cells, B cells [13,14], and NK cells [15]. This review will additionally discuss emerging data on antifungal contributions from lesser studied unconventional or innate-like

lymphocytes such as γδ T cells, MAIT cells and iNKT cells, which display attributes of both innate and adaptive immunity, and ILC. Although numerically less abundant than their conventional counterparts in circulation, innate-like lymphocytes tend to be more abundant in mucosal barrier sites, where they display rapid and potent antimicrobial responses and are thought to play an important role in immuno-surveillance [16,17]. Unconventional lymphocytes are not classically MHC-restricted and express a range of pattern recognition receptors (PRRs) and can therefore rapidly recognise conserved microbial antigens. Some unconventional lymphocyte subsets express T cell receptor (TCR) chains generated similarly to conventional TCRs by genetic recombination [18]. However, these chains often possess invariant antigen-binding domains, e.g. the Vα7.2 chain expressed by human MAIT cells, and the Vγ9Vδ2 TCR expressed by the most abundant γδ T cell subset in human blood [19], meaning that these invariant cells are among the most abundant immune cells, on an antigen-specific level. Unconventional lymphocyte subsets recognise microbe-derived or autologous antigens and respond within hours of detection but also demonstrate features of memory T cells, such as expression of memory markers. Unconventional lymphocytes have been shown to play important roles in immune responses against infections caused by bacteria, viruses and parasites [19–21] and are therefore likely to play a similar important role in host defence against fungal pathogens.

2. Fungal recognition by the immune system

Microorganisms expose highly conserved pathogen-associated molecular patterns (PAMPs) that are readily detected by the PRRs of innate immune cells. Important and well known fungal PAMPs include the cell wall constituents β-1,3-glucan, mannans and chitin [22]. Furthermore, multiple antigenic structures are found on fungi which may trigger an adaptive immune response in the infected host [7,14]. These comprise cell wall carbohydrates, but also proteins such as proteases and glycosidases. The proteases can also be recognised by protease-activated receptors (PARs), as previously reviewed [23].

Important PRRs that detect fungal PAMPs are Toll-like receptors (TLR), C type lectin receptors (e.g. dectin-1, dectin-2, DC-SIGN, mannose receptor), NOD-like receptors (NLRs), damage-associated molecular patterns (DAMPs) and others such as RAGE, and ficolins, soluble lectins which bind fungal conidia and activate the lectin pathway of complement. Notably, the antigenic structures exposed by different fungal species vary greatly. In addition, some fungal species undergo morphological switches during infection which are associated with significant changes in the exposed antigens and PAMPs. For example, the cell wall of the initially inhaled conidia (asexual spores) of the ubiquitous mould *A. fumigatus*, which causes approx. 90% of all invasive aspergillosis cases, is very different from the cell wall of the hyphae that are formed later on and which invade the tissue [24,25].

Multiple PRRs are activated by fungal PAMPs, as reviewed previously [26], depending on the fungal species and its morphological stage. Signals from these PRRs are integrated to produce an effective immune response, inducing production of a complex array of pro- and anti-inflammatory cytokines and chemokines. Such factors enable recruitment and activation of other immune cells, amplifying and diversifying the immune response, e.g. dendritic cell (DC) sensing of multiple fungal antigens and integration of these signals for subsequent maturation, activation of transcriptional programmes and orchestration of the adaptive immune response. PRRs are commonly expressed by innate cells such as neutrophils, monocytes, macrophages, DCs, and even by epithelial and endothelial cells, which can contribute to immune activation in response to fungal antigens, as expertly reviewed [7,27]. Defects in PRRs affect antifungal immunity, for example, dectin-1 knockout mice challenged with *A. fumigatus* display uncontrolled fungal growth in the lung and impairments in neutrophil recruitment and function, and defective production of cytokines and chemokines, e.g. IL-1α, IL-1β, TNFα, CCL3, CCL4, CXCL1 as well as IL-17 [28]. Dectin-1 knockout mice

also show an abrogation of DC function in mesenteric lymph nodes, resulting in defective CD4$^+$ T cell co-stimulation and substantial increases in CD4$^+$ T cell apoptosis in a mouse model of gastrointestinal tract infection with *C. albicans* [29].

This early anti-fungal immune response mediated by PRR signals activates potent first-line innate defence mechanisms such as phagocytosis, degranulation of antimicrobial peptides, production of reactive oxygen species (ROS), and neutrophil extracellular traps (NETs). If fungal growth cannot be limited by these innate means, the next step is activation of adaptive immune responses via antigen presentation to trigger a more specific anti-fungal response.

3. The role of conventional lymphocyte subsets in antifungal immunity

3.1. CD4 T cells

Both innate and adaptive arms of immunity are important in control of fungal invasion, with the latter arm responsible for maintaining immunological memory. The importance of CD4 T helper cell function in antifungal immunity is highlighted by the increased occurrence and severity of fungal infections in HIV infected individuals who develop AIDS, where profound loss of CD4 T cells confers susceptibility to opportunistic infection by various fungal pathogens, e.g. *Candida, Cryptococcus, Pneumocystis, Aspergillus, Penicillium, Alternaria* and *Rhodotorula* species [10,11].

CD4 T cells are primarily activated by antigen presenting cells, which present fungal antigens on MHC class II molecules and supply costimulatory and cytokine signals which trigger polarisation of naive CD4$^+$ T cells into various T helper (Th) subsets. Successful control of fungal infections has been shown to involve a fine balance between Th cell subtypes, namely Th1, Th2, Th9, Th17 and regulatory T cells (Treg), all of which play a role in the immune response to fungi, though some contributions can be pathogenic as well as beneficial [30,31]. The Th1 response provides protective immunity against fungi through enhancing the functions of phagocytic cells via production of IFNγ, TNF and GM-CSF, and by promoting B-cell production of opsonizing antifungal antibodies. Mouse models have demonstrated the protective effects of Th1 immunity, e.g. adoptive transfer of *Aspergillus*-pulsed DCs increased resistance to invasive aspergillosis in murine allogeneic hematopoietic stem cell transplant (allo-SCT) recipients by activating IFNγ-producing T lymphocytes [32], transfer of *Aspergillus*-specific Th1 cells conferred protection against invasive aspergillosis in neutropenic mice [33] and T cell derived IFNγ levels correlated with the clearance of *Histoplasma capsulatum* from the lungs [34].

Environments rich in cytokines IL-1, IL-23 and IL-6 select for polarisation of Th17 cells. Th17 cells release IL-17A, IL-17F and IL-22. IL-17A promotes neutrophil recruitment and plays a critical, non-redundant role in resolution of *C. albicans* infections, as demonstrated by knockout mouse models and cases of gene defects in the IL-17 pathway [35]. *Aspergillus fumigatus* however, appears to trigger a more Th1 predominant response and shows a lesser IL-17 response than *C. albicans* [36]. IL-17 is a pleiotropic cytokine and can contribute to pathogenic inflammation as well as pathogen clearance. For example, mice with IL-23 defects show reduced fungal burdens after intragastric *C. albicans* infection or intranasal *A. fumigatus* infection, suggesting that Th17 cells may be detrimental in antifungal host defence [37]. Patients with inborn deficiencies of either Th1 or Th17 pathway molecules exhibit increased incidence of fungal infections, suggesting a crucial role for these effector cells in antifungal immunity [38,39].

Th2-type responses, characterised by expression of IL-13, IL-4, IL-5, IL-10, IL-13 and IL-24 are generally ineffective for fungal pathogen clearance and can promote fungal persistence and trigger detrimental allergic inflammation, for example IL-5 production from Th2 cells and eosinophil influx into the lungs drives allergic bronchopulmonary aspergillosis [30]. Th2 cytokines IL-4 and IL-10 have been associated

with disease progression in mouse infection models [33]. Vaccination of mice using various *Aspergillus* antigens shows that such antigens drive both protective Th1 and deleterious Th2 responses, and that Th1 responses are protective against subsequent pathogen exposure.

3.2. CD8 T cells

CD8 T cells respond to fungal antigens, either via professional antigen presenting cells or by direct stimulation of CD5, CD23, CD56 and TLRs [40,41]. DC detect fungal antigens via integrated PRR signals, process and cross-present these antigens on MHC class I molecules, and drive a cytotoxic CD8 T cell phenotype, characterised by production of cytokines IFNγ, TNF, GM-CSF, and generation of protective memory responses to *Aspergillus fumigatus* [42]. CD8 T cells can produce IL-17 and rescue CD4-deficient mice from lethal fungal pneumonia infection [43]. CD8 T cells have also been shown to have protective effects in CD4-deficient mouse models of infection with *C. albicans* [44], *C. neoformans* [45], *H. capsulatum* [46] and *P. carinii* [47] and can maintain memory function in the absence of CD4 T cells or fungal antigen exposure [48]. *Aspergillus*-reactive CD8 T cells were protective in an immunocompromised mouse model of invasive pulmonary aspergillosis, demonstrating cytotoxic function and extending overall survival time when adoptively transferred into *A. fumigatus*-infected immunocompromised mice [49]. CD8 T cells therefore appear to play a protective, CD4-independent role in antifungal immunity and are under investigation as potential cell-based immunotherapies to control fungal infections [41].

3.3. B cells

Upon sensing fungal antigens, B cells undergo class switching and produce various classes of antibodies with direct and indirect fungicidal effects, as expertly reviewed previously [14,50]. Direct effects include antibody binding of fungi and inhibition of fungal growth and metabolism [51], and indirect methods include antibody-mediated activation of microbiocidal immune effector pathways, e.g. complement and opsonisation. Various fungal antigens have been shown to elicit protective antibodies against the major fungal species, e.g. *A. fumigatus*, *C. albicans*, *C. neoformans*, *H. capsulatum*, *P. brasiliensis* and *Pneumocystis spp.* [50]. For example, *A. fumigatus* proteins trigger the production of *Aspergillus*-specific IgG antibodies in invasive aspergillosis [52].

B cells have also been demonstrated to provide help to anti-fungal T cells, in an antibody independent manner, by providing costimulatory signals in an in vitro model of *C. albicans* infection [53]. In this model, B cells responded to *C. albicans,* produced IL-6 and GM-CSF, and provided strong costimulatory signals to naive T cells via CD80/CD86 in an MHC-dependent manner [53]. The observation that patients with agammaglobulinemia exhibit normal antifungal immunity, while those undergoing B cell-depleting therapies show increased incidence of fungal infection suggests that this B cell help of effector T cells presents an important facet of the B cell-mediated antifungal immune response.

4. Uncovering the role of novel unconventional lymphocyte subsets in anti-fungal immunity

4.1. NK cells

NK cells do not express T cell receptors, but instead are defined by expression of CD56 in the absence of CD3. NK cells respond to fungal antigens from numerous species and display direct antifungal action via release of microbiocidal molecules such as perforin, and indirect antifungal action by cytokine release, as detailed in recent reviews [15,26]. In the setting of *Aspergillus* infection, NK cells are potent early producers of IFNγ, with NK cell depleted mice with invasive aspergillosis showing lower levels of IFNγ in the lung and higher lung fungal load, though NK cell depletion had no further detrimental effect in IFNγ deficient mice, suggesting that IFNγ production is the main contribution of NK cells to

antifungal immunity [54]. Human NK cells mediate damage to *Aspergillus* via release of soluble factors, i.e. NK cell-derived perforin [55] and IFNγ [56], which show antifungal properties. In addition, it is noteworthy that, vice versa, *A. fumigatus* can induce immunosuppressive effects on host NK cells by secreting gliotoxin, aflatoxin, galactosaminogalactan and chitin [57]. Furthermore, it was shown that in vitro secretion of IFNγ and GM-CSF by NK cells co-incubated with *Aspergillus* hyphae was significantly lower compared to levels in the culture supernatant of NK cells incubated without the fungus [58]. NK cells respond to *Aspergillus* hyphae but not resting or germinating conidia, suggesting that NK cells respond to fungi at a more advanced stage of invasion [15,58], as summarised in Fig. 1. NK cells required cell-pathogen contact and priming with IL-2 to mediate fungal damage. The main fungal species reported to interact with unconventional lymphocyte subsets are summarised in Table 1.

NK cells play an important role in the orchestration of the innate immune response against *A. fumigatus*. Zhang and colleagues recently showed that NK cell activity and IFNγ secretion in response to *A. fumigatus* is controlled by M1 type macrophages and galectin-9 [59]. Furthermore, Weiss et al. described a close crosstalk of NK cells and DCs [60], whereby DCs are able to recognise a broad spectrum of fungal components and thereby initiate NK cell activation. NK cells have also been reported to recognise fungal components via several receptors, including the NKp30 receptor, which recognises β-1,3-glucan and triggers perforin release [61,62], and the NKp46 receptor which binds *C. glabrata* adhesins Epa1, Epa6 and Epa7 and mediates fungal killing [63]. NK cells have been reported to mediate cytotoxic effects in response to other fungal species, including *P. brasiliensis* [64]. CD56 has also been shown to play a role in *A. fumigatus*-mediated NK cell activation and proinflammatory cytokine production (CCL3, CCL5) in humans and blocking CD56 inhibited this response [65]. NK cells are thought to contribute to pathologic cytokine storms in the condition of disseminated histoplasmosis*,* hemophagocytic lymphohistiocytosis, but appear to be reduced in number and non-functional at later stages [66].

Patients after allo-SCT run the highest risk of developing invasive pulmonary aspergillosis. Interestingly, in NK cells isolated from patients after allo-SCT, decreases were observed in CD56 binding to live *Aspergillus* germ tubes and relocalisation to the fungal contact side [67]. This deficiency was correlated to the administration of corticosteroid therapy, which also negatively influenced the secretion of chemokines MIP-1α (CCL3), MIP-1β (CCL4), and RANTES (CCL5). In addition, actin dysfunction was observed in NK cells after allo-SCT until 180 days post-transplant, as shown by a reduction in F-actin content [67].

4.2. γδ T cells

γδ T cells are the prototypic population of unconventional or innate-like T cells, so called because they exhibit characteristics of both innate and adaptive immunity [19]. Human γδ T cells are involved in immunosurveillance and host defence against infection and malignancy and are defined by expression of a TCR composed of γ and δ chains [17]. Six main subsets of human γδ T cells have been described (Vδ1-Vδ6) defined based on δ-chain usage, with the Vδ1, Vδ2 and Vδ3 subsets being most abundant in circulation [68]. Human γδ T cells differ in several fundamental respects to their mouse counterparts, where subsets are usually categorised by γ-chain use. For example, the predominant human circulating subset of mycobacteria-reactive Vγ9Vδ2 T cells is found only in higher primates and not in mice, and likewise humans do not possess the predominant tissue-resident γδ population of dendritic epidermal T cells (DETC) described in mice. IL-17 production by mouse γδ T cells appears to be the result of an innately programmed "γδ17" cell subset arising in early development, whereas IL-17 production by human γδ T cells appears to occur due to context dependent peripheral polarisation [69]. Care should therefore be taken when interpreting γδ T cell studies using mouse models in the context of human disease.

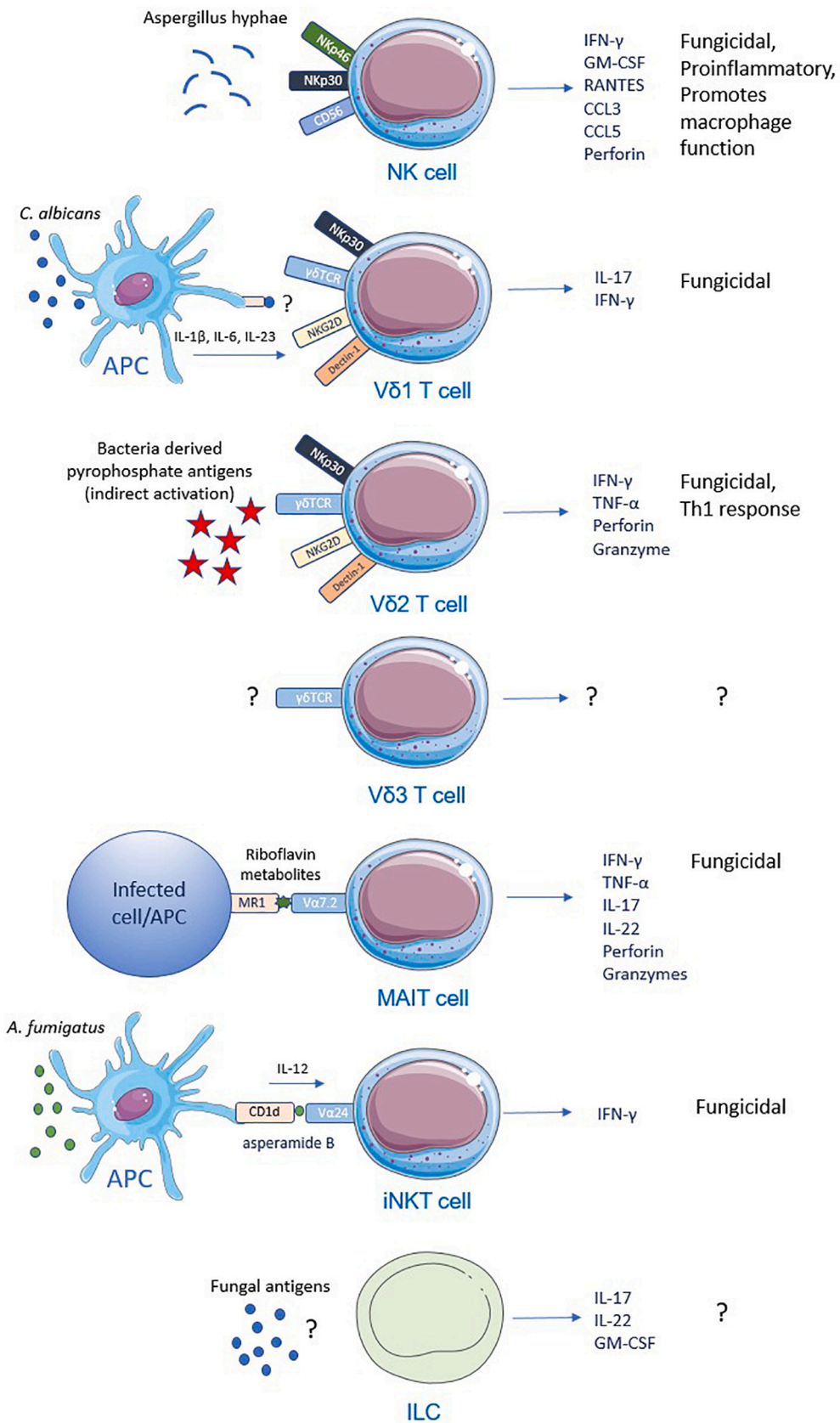Human γδ T cell subtypes differ in their antigen specificities,

Fig. 1. Known antifungal effects of unconventional T cell subsets. APC = Antigen presenting cell.

Table 1
Fungal antigen recognition by unconventional lymphocyte subsets.

	NK cells	Vδ1 T cells	Vδ2 T cells	MAIT cells	iNKT cells	ILC
Candida spp	*C. albicans* binds NKp30, mediates fungal killing [61,62]; *C. glabrata* binds NKp46, mediates fungal killing [63]	Produce IL-17 and IFNγ, proliferate [73,84–86]	Minimal response [84,85]	Upregulation of IFNγ, TNFα and IL-17 [108]	Indirect activation via DC-derived IL-12, produce IFNγ [111]	Produce IL-17 in mouse model of oral candidiasis [115]
Aspergillus fumigatus	Respond to hyphae but not resting conidia, release IFNγ, TNFα [56,58]; CD56 involved in NK activation [65]		Phosphoantigen reactive Vγ9Vδ2 T cell clones exposed to *A. fumigatus* express TNFα [83]	Respond within 4 h culture with *A. fumigatus*, *A. flavus* or A. *terreus* conidia by upregulating activation markers CD69 and CD107a [104]	Indirect activation via DC-derived IL-12, produce IFNγ [111]; Recognises asperimide B and contributes to mouse model of *Aspergillus* hypersensitivity [112]	
Cryptococcus neoformans	Binds NKp30, mediates fungal killing [62]					
Paracoccidioides brasiliensis	Recognises and destroys fungi and infected cells [64]		Expand in response to protein antigen [89]; Support B cell expansion and antibody production [87]			
Histoplasma					Indirect activation via DC-derived IL-12, produce IFNγ [111]	
Alternaria					Indirect activation via DC-derived IL-12, produce IFNγ [111]	

All studies performed using human models, unless otherwise stated.

functional responses and anatomical abundance, but share a propensity for rapid responses to antigen recognition, characterised by production of cytokines (particularly IFNγ), chemokines and cytotoxic effector molecules. The predominant circulating γδ T cell subset bears a semi-invariant Vγ9Vδ2 TCR with a public germline encoded CDR3γ sequence and a more diverse CDR3δ sequence [70], which recognises low molecular weight non-peptide prenyl pyrophosphate antigens including (E)-4-Hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP), a metabolite produced by many microbes, and isopentenyl pyrophosphate (IPP), an isoprenoid biosynthesis self-antigen which accumulates in large amounts in abnormal cells and in response to alkyl amines and aminobisphosphonate drugs [71]. Upon recognition of HMB-PP or IPP, Vγ9Vδ2 T cells rapidly expand and express high levels of Th1 type cytokines [72]. Vδ1 and Vδ3 subsets are more abundant in mucosal sites and are observed to be elevated in various infections, e.g. HIV [73,74] and CMV [75]. The precise antigens recognised by Vδ1 and Vδ3 subsets are unknown, but subsets of both cell types have been shown to respond to CD1 molecules, which present glycolipid antigens [76–78]. Vδ3 cells are abundant in healthy human liver [79] and have been shown to play a role in chronic cytomegalovirus infection [75,80,81]. Although γδ T cells express a TCR, they largely recognise antigens in an MHC unrestricted manner. They can also be activated via NKG2D ligation of stress-induced molecules e.g. MICA and MICB. Human γδ T cells can also act as antigen presenting cells [82] and promote IL-22 but not IL-17 expression by intestinal CD4 T cells [83].

In terms of anti-fungal immunity, human γδ T cells have been reported to respond to stimulation with various fungal species, e.g. *A. fumigatus* [84], *C. albicans* [85–87] and *P. brasiliensis* [88]. Vδ1 T cells appear to be more responsive to *C. albicans* in terms of proliferation, IFNγ and IL-17 production compared to Vδ2 T cells, with the latter responding preferentially to pyrophosphate-producing bacterial antigens [85,86]. *Aspergillus* and *Candida* do not express the prenyl pyrophosphate pathway intermediate molecule HMB-PP, which is a potent stimulator of Vγ9Vδ2 T cells [89], which likely accounts for this observation. Phosphoantigen reactive Vγ9Vδ2 T cell clones have been reported to produce substantial amounts of TNFα in response to

stimulation with a water-soluble cellular extract from *A. fumigatus* [84], however the identity of the antigen recognised remains unknown. Vδ1 T cells from both HIV$^+$ patients and healthy donors were observed to respond to *C. albicans* [85,87]. Vδ1 T cells are not depleted in HIV infection, in fact, Vδ1 T cells are elevated in the blood of HIV$^+$ individuals and even more so in HIV$^+$ cases with candidiasis [85,87]. IL-17 production by Vδ1 T cells in response to *C. albicans* stimulation in vitro relies on the presence of dendritic cell-derived IL-1β, IL-6, and IL-23 [87]. Cell-cell contact was important for this process, since IL-17 expression from Vδ1 cells could not be recapitulated using these cytokines in the absence of dendritic cells, or when Vδ1 T cells and dendritic cells were separated by a semi-permeable membrane. Human γδ T cells stimulated in vitro with *P. brasiliensis* produced cytokines capable of supporting antibody production and expansion of committed B cells [88]. Recognition of *P. brasiliensis* was observed in Vγ9Vδ2 T cells specifically [90], driving cell proliferation which was abrogated in the presence of proteinase, suggesting recognition of a protein-based fungal antigen, rather than a contaminating bacteria-derived pyrophosphate antigen.

Mouse models demonstrate an overall protective role for murine γδ T cells in antifungal immunity, thought to be mediated predominantly by the γδ17 subset [91]. Murine models of *Candida* infection in γδ T cell-depleted mice show abrogations in inducible nitric oxide synthase production [92] and neutrophil recruitment [93], which result in failure to clear the pathogen. A mouse model of *Pneumocystis carinii* infection demonstrated faster fungal clearance from the lungs of γδ T cell-deficient mice, which was linked with improved CD8 T cell mobilisation to the lung and higher IFNγ, suggesting that murine γδ T cells impede CD8 T cell effector function in this setting [94]. This suggests a regulatory role for murine lung γδ T cells, in prevention of excessive tissue inflammation.

Murine and human γδ T cells express fungal receptors dectin-1, TLR1 and TLR2 [87,95,96], with expression particularly notable in IL-17-producing γδ T cell subsets. In mice, IL-17 plays a critical role in anti-fungal immunity in neutrophil recruitment, which at least partly accounts for the predominantly protective role for γδ17 cells in fungal

infection models [91]. In humans, neutrophil recruitment in response to fungal antigens occurs via CXCL8, the gene for which is lacking in mice, suggesting that IL-17 may play a less critical role in neutrophil recruitment than in the murine setting [19]. Intriguingly, dectin-1 expression by mouse and human γδ T cells appears to be particularly abundant in the liver, where it is associated with IL-17 and IL-22 production and tissue repair and regeneration under conditions of non-pathogenic sterile inflammation [96]. Addition of dectin-1 ligand zymosan promotes this regenerative process [97]. Under such conditions, an inhibitory role for dectin-1 is described, where dectin-1 suppresses TLR4 signalling in hepatic inflammatory and stellate cells to protect against chronic liver disease. Both human and mouse γδ T cells have been shown to play a role in wound repair, which further supports a role for these cells in barrier repair as well as in pathogen defence [98,99].

4.3. MAIT cells

Mucosa-associated invariant T (MAIT) cells are a subset of unconventional αβ T cells which express an invariant Vα7.2 T cell receptor alpha chain (TRAV1–2 linked with either TRAJ33, TRAJ12 or TRAJ20 in humans and TRAV1-TRAJ33 in mice) paired with a beta chain strongly biased toward TRBV6 family members and TRBV20–1 [100]. Some junctional diversity was noted in the TCRα chain in humans and cattle, whereas no N additions or trimming were noted in most murine sequences. MAIT cells sense microbes through recognition of microbe-derived vitamin B2 metabolites presented by the MHC class I-related molecule, MR1 [101]. MAIT cells express high levels of the C-type lectin CD161 and commonly express CD8. MAIT cells are abundant at mucosal surfaces, including the skin, intestinal tract, lung, omentum and liver and respond to antigens derived from the riboflavin biosynthesis pathway, used by many different species of bacteria and fungi [102]. MAIT cells can also be activated by cytokines alone (e.g. IL-7, IL-12, IL-15, IL-18), however this mode of activation is thought to play more of a role in the viral infection setting [103,104].

MAIT cells have been shown to become activated in response to several fungal species, e.g. *C. albicans, C. glabrata, S. cerevisiae, Mucorales* and *Aspergillus* [105–107]. Once activated, MAIT cells rapidly produce cytokines, including IFNγ, TNFα, IL-17 and IL-22, and rapidly acquire cytotoxic capability via production of perforin and granzymes, allowing them to kill microbially-infected cells [108,109]. Indeed, it has been observed that MAIT cells rapidly respond to co-culture with fungi (e.g. *A. fumigatus, A. flavus,* or *A. terreus* conidia) by upregulating activation marker CD69 and CD107a, a marker of lytic granule release, within 4 h [106]. Despite putative recognition of microbes via a common riboflavin biosynthesis pathway, MAIT cells show evidence of pathogen-specific responses, as evidenced by in vitro exposure to *E. coli* and *C. albicans,* which showed differences in the magnitude and sensitivity of polyfunctional responses to these two pathogens, which was influenced by the Vβ chain [110]. MAIT cell activation by fungi required presentation of riboflavin metabolites and was dependent on TCR engagement, since antibody blocking of MR1 prevented marker upregulation. MAIT cells producing IL-17 are thought to contribute to pathogenesis in chronic inflammatory diseases [111] but may play a beneficial role in antifungal immunity, where IL-17 is involved in early pathogen elimination.

4.4. Invariant NKT cells

Invariant NKT (iNKT) cells comprise a relatively rare population of T cells, defined by expression of an invariant TCR α-chain, Vα24Jα18 (TRAV10-TRAJ18) in humans and Vα14Jα18 (TRAV11-TRAJ18) in mice, paired to a restricted set of TCRβ chains (TRBV25 in humans and TRBV1, TRBV13, and TRBV29 in mice). iNKT cells become activated in response to glycolipid antigens such as α-galactosylceramide in a CD1d-restricted manner and express a combination of Th1 (IFNγ, TNFα), Th2 (IL-4, IL-5, IL-10, IL-13) and Th17 (IL-17, IL-22) cytokines and chemokines [112].

iNKT cells can be rapidly activated by fungi indirectly by IL-12 produced by APCs as a result of β-1,3 glucan detection via dectin-1 and MyD88 signalling [113]. Thus, iNKT cells can be activated by *Aspergillus, Candida, Histoplasma,* and *Alternaria* species and produce a range of cytokines, including IFNγ. Interestingly, this IFNγ production is protective during *Aspergillus* infection but detrimental in candidiasis, where glycolipid-treated mice infected with *C. albicans* showed worse survival and greater fungal burden, not seen in IFNγ knockout mice [114], and increased plasma IFNγ levels during early sepsis have been linked to subsequent development of secondary *Candida* infection [115]. iNKT cells have also been shown to be major regulators of IFNγ production by NK cells, via mTORC1 [115]. It is hypothesised that IFNγ, usually a key cytokine mediating host defence, can have a paradoxical immunosuppressive effect in certain settings. Since iNKT cells are polyfunctional cells which express many immunomodulatory cytokines upon activation, their role in fungal immunity may be more complex, and the relative levels of cytokines produced and when and where they are expressed may also impact on clinical outcomes. IL-10 production by iNKT cells has also been shown to affect *Candida* clearance in a mouse model, where suppression of phagocytic function was demonstrated [116]. Furthermore, Jα18$^{-/-}$ knockout mice, deficient in iNKT cells showed lower susceptibility to lethal *C. albicans* infection [116].

A glycosphingolipid antigen derived from *Aspergillus fumigatus,* asperamide B, was found to directly activate human and mouse iNKT cells in vitro in a CD1d-restricted manner, independently of MyD88 or dectin-1 and drove allergic airway responses and contributed to *Aspergillus* hypersensitivity in a mouse model of *Aspergillus* infection [117].

4.5. ILCs

Innate lymphoid cells (ILC) are found in the intestinal mucosa from an early developmental stage and share a common progenitor with NK cells. ILC lack a specific antigen receptor or lineage markers and are instead categorised into three main sub-groups: group 1 innate lymphoid cells (ILC1), group 2 innate lymphoid cells (ILC2) and group 3 innate lymphoid cells (ILC3), depending on transcription factor expression and effector functions [118]. It was initially thought that Th17 cells were the main IL-17 source in fungal infections, but subsequent studies have revealed important contributions from γδ T cells and ILCs [119,120]. Once activated, the ILC3 group has been shown to produce IL-17A, IL-17F, IL-22 and GM-CSF but more detailed studies are required to confirm whether these cells play a direct role in antifungal immunity [121].

5. Clinical implications and considerations for therapeutic targeting of unconventional lymphocytes

The incidence of invasive fungal infections in immunocompromised individuals is increasing [122] and so too is resistance to antifungal drugs [123], a problem exacerbated by the dearth of antifungal drugs in existence. The clinical challenge when treating opportunistic fungal infections is to control spread of the pathogen while limiting a deleterious autoimmune response. This is particularly challenging in immunocompromised individuals, e.g. stem cell transplant recipients, where the efficacy of antifungals can be impeded by drug-drug interactions and side-effects, which can prevent long term use or dose escalation. Restoration of adaptive immunity can take time in stem cell transplant recipients, therefore boosting this process via cell- or cytokine-based immunotherapies has been proposed as a therapeutic avenue to reducing invasive fungal infections [7,41,124]. Several therapies involving monoclonal antibodies and small molecule inhibitors that target components of the immune system have been licensed for the treatment of infectious and autoimmune diseases and cancer. More recently, cellular immunotherapies involving the transfer of effector cells, activated and expanded ex vivo or engineered to improve target specificity or function, have come to the forefront with T cells expressing

chimeric antigen receptors (CAR T cells) approved for the treatment of certain cancers.

Unconventional lymphocytes also offer immunotherapeutic potential, with multiple clinical trials employing adoptively transferred Vγ9Vδ2 T cells and iNKT cells ongoing in cancer patients [125–127]. To date, such trials have shown only modest success in treating cancer but importantly, have demonstrated that adoptive transfer of unconventional lymphocytes is safe and well tolerated. Human γδ T cells are a potent source of Th1 cytokines, including IFNγ, which itself has been used as an immunotherapy for invasive fungal infections [128,129] and TNFα, therapeutic depletion of which has been linked with increased incidence of invasive fungal infections [130]. This suggests that unconventional lymphocytes could potentially be used as immunotherapeutic agents in the fungal infection setting, e.g. using conserved fungal antigens or even (in the case of Vγ9Vδ2 T cells) bacteria-derived pyrophosphate antigens to activate a potent Th1 response, particularly important in protection against invasive aspergillosis [84]. Such immunotherapeutic strategies could potentially be used in combination with other treatments to counteract their deleterious side effects on antifungal immune responses. For example, Bruton tyrosine kinase inhibitors such as Ibrutinib, used in treatment of lymphoma, are associated with increased incidence of pulmonary aspergillosis, due at least in part to reduced TNFα production [131,132]. Immunotherapeutic activation of γδ T cells in this setting may have a two-fold beneficial effect – replenishing antifungal TNFα to protect against opportunistic fungal infection arising, but also acting in cancer killing capacity [133]. Whether Vδ1 or Vδ2 (or even potentially, the enigmatic Vδ3) T cells are optimal for such an approach remains to be determined, however.

Other unconventional T cells such as Vδ1 T cells, MAIT cells and ILCs express IL-17, shown to be important for *C. albicans* clearance. Unconventional lymphocytes undergo rapid expansion once activated, which is advantageous when generating antifungal cell lines for adoptive transfer approaches to treat diseases with rapid progression, e.g. invasive aspergillosis. To date, cellular therapies have used autologous cells, which drives up costs and limits the numbers of patients that can be treated. However, unconventional lymphocytes are not typically MHC restricted and therefore do not mediate allogeneic tissue rejection and are well tolerated upon adoptive transfer. Therefore, they have greater potential as an 'off-the-shelf' therapy which can be used for multiple patients.

When studying unconventional lymphocytes and their potential use as immunotherapeutic agents, it is important to consider their inherent plasticity. Human γδ T cells have been shown to play multiple roles depending on their stimulus and environment, and can even act as professional antigen presenting cells [82]. Furthermore, phenotypic differences in fungus-specific T cell profiles have been noted between circulating and mucosal-resident compartments. For example, in the case of *A. fumigatus* antigen stimulation, specific effector memory CD4 T cells derived from peripheral blood of healthy adult donors displayed a predominant Th1 phenotype whereas *Aspergillus*-specific effector memory CD4 T cells from bronchiolar lavage fluid showed a Th17 phenotype with marked production of IL-17 and little IFNγ [134]. This suggests that significant differences exist between circulating and tissue-resident T cell subsets and assessing the immune response at a single anatomical location may be misleading. Further work is therefore required to optimally harness the immunotherapeutic potential of unconventional lymphocytes.

Commensal gut microbiota have also been shown to influence antifungal immune cell functions, e.g. in a mouse model of pulmonary fungal infection, CD4 T cell polarisation was altered when mice were given vancomycin in drinking water, with significant reductions observed in IL-22 and IL-17, but not IFNγ [135]. This observation is likely to be relevant to unconventional lymphocyte function too, since many unconventional subsets are known to interact closely with bacteria at mucosal sites [84]. Indeed, in an ocular mouse model of *C. albicans* infection, the commensal bacterium *Corynebacterium*

mastitidis was shown to trigger an IL-17 response from γδ T cells in the ocular mucosa which induced neutrophil recruitment and release of antimicrobial peptides which mediated protection from *C. albicans* infection [136]. Such studies highlight the potential use of microbial antigens to harness and direct unconventional T cell effector functions to aid antifungal immunity. Indeed, it is known that MAIT cells may be selectively activated or inhibited in vitro, when treated with riboflavin precursors or folate derivates, respectively [102,137] and that pyrophosphate antigens such as HMB-PP activate a Th1-like response from Vγ9Vδ2 T cells [72]. As summarised in Table 1, few fungal antigens have been described which directly activate unconventional lymphocytes, therefore indirect activation using other microbial antigens may present a more accessible approach to promoting antifungal immunity.

6. Conclusion

Unconventional lymphocyte subsets remain understudied and are often overlooked as immune effectors, but recent work shows that many of these cells respond to fungal species which drive IFDs and therefore warrant further investigation as potential immunotherapeutic targets. Unconventional lymphocytes possess several advantages over conventional cells for use as cellular therapeutics, including the fact that they are not MHC restricted therefore therapies do not need to be autologous, they elicit rapid and potent responses which are subject to tight regulation in the body, and appear to be well tolerated upon adoptive transfer. More research is needed before the antifungal properties of unconventional lymphocytes can be successfully harnessed for immunotherapy and issues such as cost will need to be addressed, however the advantages offered by unconventional lymphocytes mean that such immunotherapies could prove less costly than those currently in development using conventional lymphocyte approaches. Unconventional lymphocytes show promise as anti-cancer immunotherapies and may likewise have a place in future treatment of invasive fungal diseases.

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